



PATHOBIOLOGY PHARMACOLOGY SUMMARY

SideKick



YOUR BEST FRIEND



General & Local Anaesthesia

General Anaesthesia:

- **The target of general anesthesia is to:**
 - lose consciousness
 - lose sensation
 - relax muscles.
- **General anesthesia has 4 stages:**
 - I. **Stage 1:** analgesia
 - II. **Stage 2 :** excitement
 - III. **Stage 3:** surgical anesthesia
 - IV. **Stage 4 :** medullary paralysis

We need to skip stage 2 as fast as possible and never reach step 4 “stay in stage 3”

Pre anesthetic medication:

➔ for smooth induction of anesthesia

1- **Anti-cholinergic drugs:** (scopolamine)

For decreasing airway secretions – prevention of bradycardia- counteract respiratory depression caused by morphine.

2- **Benzodiazepines:**

To induce sedation and relieve anxiety

3- **H1 blockers** (Doxylamine): anti-allergic “can prevent bronchospasm caused by histamine”

H2 blockers (cimetidine): to decrease gastric acidity

4- **Anti-emetic drugs** (metochlopramide)

5- **Opioid analgesics** (morphine & pethidine)





General Anaesthesia

Induction by IV drugs

(these IV drugs can also be used for short surgical procedures)

Maintenance by inhalational

Mechanism of action:

- 1-change the membrane fluidity of the nerve cells.
- 2- enhance action of :GABA – glycine & inhibit action of :serotonin – acetylcholine – glutamate.

Induction of general anesthesia:

1. Thiopental: IV barbiturate, enhance effect of GABA

- 1- Rapid onset of action (ultra-short barbiturate) – short duration (2-5 minutes)
- slow recovery (up to 24 hrs.)
- 2- Potent anesthetic, no analgesic effect.
- 3- Its elimination occurs by redistribution, so it has slow recovery.

Disadvantages:

Decrease BP – bradycardia- cough- apnea – laryngospasm
(Parasympathetic like effects)

2. Ketamine: acts as NMDA antagonist → N.methyl.D. aspartate receptor (glutamate acts on this receptor)

- 1- slow onset of action , short duration , slow recovery.
- 2- good analgesic but not used for induction of anesthesia .
- 3- **Dissociative anesthesia** (consciousness – no pain) → used in short surgical procedures as burn redressing – endoscopy.
- 4- Can be used in children, elderly.

Disadvantages:

Increase sympathetic flow, increase BP, cardiac output, cerebral flow (so it is contraindicated in hypertension and stroke – it can cause hallucination)





3. Propofol:

- 1-rapid onset, short duration of action, rapid recovery.
- 2- Anesthetic not analgesic.
- 3- It has antiemetic action, so post-operative nausea and vomiting are lessened.
- 4-can be used for sedation by IV infusion "controlled ventilation" in ICU.

Disadvantages:

Dose related hypotension "decreased BP" – bradycardia – respiratory depression.

Maintenance of general anesthesia (Inhalational anesthesia):

Rate of onset and recovery:

- it depends on blood solubility of the drug. (blood gas coefficient)
- Drugs with high blood gas solubility ratio have slow onset of action and slow recovery (& vice versa).

Potency:

- It depends on MAC (minimal alveolar concentration)
- Minimal concentration of the drug in alveoli needed for anesthesia of 50% of patients.
- MAC value is additive → can be modulated by age of patient, pre anesthetic medications.

Inhalational anesthetics less commonly used:

	Rapid / slow induction - recovery	Anesthetic / <u>analgesic</u>	Effect on CVS	Major side effect
Nitrous oxide	rapid	Potent <u>Analgesic</u> , low potency of anesthesia	No effect	neutropenia
Halothane	rapid	Potent anesthetic	Cardiac arrhythmia	Hepatitis
methoxyflurane	slow	Potent <u>analgesic</u>	Cardiac stability	nephrotoxicity
Enflurane	rapid	Potent anesthetic		nephrotoxicity





Inhalational anesthetics currently used:

Sevoflurane	Desflurane	Isoflurane
- extremely rapid onset of action - less potent (Higher MAC) - Non-irritant (used in Bronchial Asthma) - Used in children - used for induction - Doubtful Nephrotoxicity	- extremely rapid onset of action - the least potent (Highest MAC) - Irritant (not used in Bronchial Asthma)	- rapid onset of action - most potent (low MAC) - less-irritant (used in Bronchial Asthma)

* All of them:

- cause $\downarrow\downarrow$ BP , $\downarrow\downarrow$ COP , $\downarrow\downarrow$ PVR
- $\uparrow\uparrow$ cardiac sensitivity to catecholamines
- $\uparrow\uparrow$ cerebral blood flow
- ++ Neuromuscular blockade

-Halothane – Sevoflurane

➔ induction of anesthesia in children because they are non irritant gases – can be used in masks.

- Sevoflurane

➔ increase fluoride production – nephrotoxicity.

Local Anaesthesia

Classification of LAs depends on its structure:

- **Aromatic ring** (hydrophobic group) + **Intermediate group** (ester or amide) + **Amine group** (ionizable)

Routes of administration:

- 1- Surface anesthesia ➔ topical gel , spray
- 2- Infiltration anesthesia ➔ subcutaneous injection of the drug.
- 3- Nerve block anesthesia ➔ injection of the drug around nerve trunk proximal to the area of anesthesia.
- 4- Spinal anesthesia ➔ injection of the drug in epidural space.





Factors affecting absorption of LAs:

- 1- Dose: increasing dose will increase absorption.
- 2- Site of injection: increase vascularity of the site will increase absorption.
- 3- Presence of vasoconstricting agent (adrenaline):
 - enhance LA conc.
 - prolong LA effect.
 - reduce rate of systemic absorption and systemic toxicity.

Factors affecting onset, duration and intensity of neural blockade:

- 1- Lipid solubility: if increased → penetration of the nerve cells will increase which lead to faster onset of action.
- 2- Dose: if increased, duration of action will increase.
- 3- Tissue PH: when it is acidic, LAs (which are weak bases) will be ionized → can't cross the cell membrane.
- 4- Presence of vasoconstricting agent: prolong duration.
- 5- Protein binding: if increased → increase duration of action.

Metabolism of LAs:

- Ester group** → pseudocholinesterase = short duration of action
Amide group → liver microsomal enzymes = long duration of action

Mechanism of action:

Blockade of sodium channels in nerve cells.

Differential sensitivity to LAs:

- 1-fiber diameter: smaller nerves are affected before larger ones. (C fibers before A fibers)
- 2- myelination : myelinated ones before unmyelinated ones.
- 3-use dependant block: fibers with higher firing frequency are more sensitive than others.

Local Adverse effects:

- 1- Irritation and inflammation.
- 2- Vasodilatation except cocaine causes vasoconstriction.



Systemic adverse effects:

1-CNS:

- Restlessness,
- Tremors ,
- Convulsions due to inhibition of inhibitory neural activity.

2-CVS:

- Bupivacaine is cardiotoxic.

3- Allergic reactions:

- Caused by Ester group due to their metabolism into PABA

VIP:

- In case of liver diseases both ester and amide groups will be affected.
- Ester group is preferred in pregnancy due to short duration of action.



Treatment of Gout

Treatment of Gout:

Non pharmacological	Pharmacological
- Decrease weight - Control hyperlipidemia - Decrease purines in diet - Review other medications (salicylates and diuretics decrease uric acid excretion)	Treat acute attack Decrease serum uric acid to prevent recurrence and kidney damage

I] Treat acute attack of gouty arthritis:

	NSAIDs	Colchicine	Corticosteroids
	- Naproxen, - Sulandec, - Indomethacin	Given 12-36 hrs. from start of attack	-intraarticular & systemic prednisone
mechanism	1- analgesic 2- anti-inflammatory 3- decrease phagocytosis of urate crystals	1- inhibit microtubules in neutrophils, decrease recruitment and phagocytosis 2- decrease TNF alpha from macrophages 3- decrease IL8 (chemotactic)	
uses	Acute attack	1- acute attack treatment 2- prophylaxis against recurrent attack 3- mediteranian fever	Acute attack
Contraind.	- renal failure - peptic ulcer	- renal failure	- peptic ulcer
ADR		1- GIT: diarrhea, N & V 2- BM suppression 3- myopathy in renal impairment	*rebound symptoms if not gradually withdrawn





II] Prevent Recurrent attack (patient w/ tophi & nephropathy):

	Allopurinol	Uricosuric drugs	
	Liver → oxipuranol (long acting)	Probenecid	Sulfinpyrazone
mechanism	Xanthine oxidase inhibitor, inhibit conversion of xanthine to hypoxanthine, and hypoxanthine to uric acid	Decrease uric acid reabsorption in kidney tubules and increase excretion	
			+ antiplatelet
uses	1- recurrent attacks 2- tophi 3- uric acid stones 4- hyperuricemia with renal impairment or in elderly 5- before cytotoxic chemotherapy and in lympho/myeloproliferative diseases	In patients intolerant to allopurinol in high doses <i>(low doses will decrease secretion and increase blood concentration. Low dose aspirin has the same effect and will decrease uric acid secretion)</i>	
ADR	1- precipitate acute attack (due to release from stores) <i>*Decrease risk by combining with low dose NSAIDs or Colchicine</i> 2- Allergic reaction → maculopapular rash 3- Hepatotoxicity	1- precipitate uric acid crystals <i>*Decrease risk by fluid intake and alkalization of urine</i>	
		2- decrease renal excretion of other drugs e.g. - Penicillin - NSAIDs - cephalosporins	2- GIT upset
Contra-indications		1- renal impairment, stones, elderly	
			2- peptic ulcer 3- w/anti-coagulants





Immunosuppressive Agents

1-Corticosteroids:

Hydrocortisone, prednisone,

Prednisolone, methylprednisolone

Mechanism: 1-inhibit inflammation

-decrease PG, cytokines, histamine

-decrease T-cell proliferation

-decrease activity of neutrophil/macrophage (rest)

2-changes in cell traffic:

-increase neutrophils (but resting)

-decrease monocytes, lymphocytes

-increase T-cell sequestration in BM

Uses: 1-Allergic reaction e.g. asthma

2-Collagen diseases e.g. SLE, RA

3-transplant rejection +cyclosporine
(induction, maintenance, rescue)

ADR: 1-avascular necrosis of hip and shoulder

2- Long term CTS: DM, HTN, hyperlipidemia

2-Cyclophosphamide:

Mechanism:

1-alkylating agent inhibit DNA duplication at pre-mitotic phase

2-decrease Ab production (B cells)

impair delayed hypersensitivity (T cells)

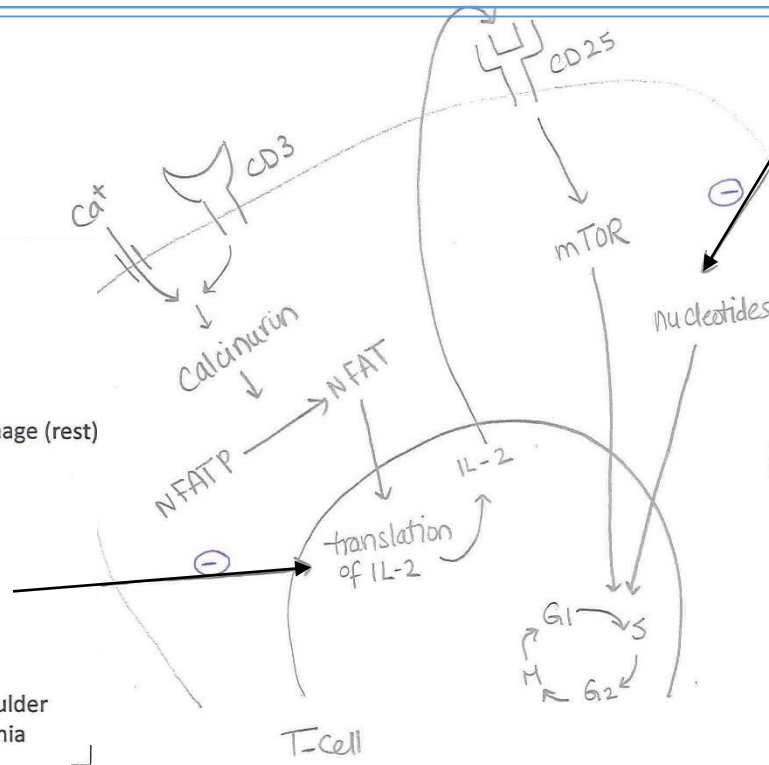
Uses: aggressive autoimmune disease +CTS

ADR:

1-increase risk of infection

activation of latent virus

2-increase risk of bladder cancer (by metabolite acrolein)



3-Azathioprine: T>B

Mechanism: metabolite 6MP is purine analogue, interfere w/ DNA synthesis

Uses:

1-Collagen Diseases e.g. SLE, RA

2-Transplant rejection +CTS
(acute rejection)

ADR:

1-increase risk of infection

dose related granulocytopenia &
thrombocytopenia

2-GIT nausea & vomiting at high dose

3-hepatic dysfunction

Kinetics:

1-eliminated by thiopurine methyltransferase (TPMT) → measure activity to prevent toxicity

2-6MP eliminated by xanthine oxidase →
allopurinol leads to toxicity

Inosine monophosphate dehydrogenase inhibitors:

(Mycophenolate Mofetil/ MPA)

Mechanism: non competitive binding to IMD, inhibit "de novo" guanosine synthesis in T, B, GIT cells

Uses:

Alternative to azathioprine if it fails or BM toxicity occurs

ADR:

1-leukopenia and anemia in high doses

2-GIT nausea, vomiting, diarrhea (most common)





Target of Rapamycin Inhibitors/Sacrolimus:

Mechanism: inhibit mTOR, delay G1-S transition, and 2nd phase of t-cell activation

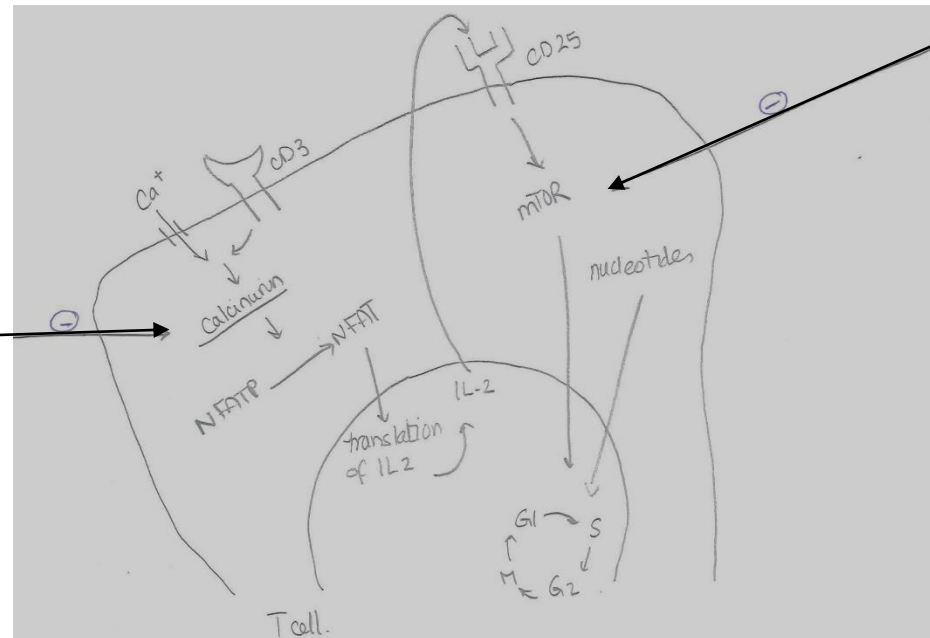
Uses: renal transplantation

ADR: 1-augment CNI nephrotoxicity

2- increase cholesterol and TAG

3-supress blood elements and delay wound healing

Calcineurin
Inhibitors



Target of
Rapamycin

Calcineurin Inhibitors

Cyclosporine

Tacrolimus (more potent, oral/topical)

Site: cyclophilin

immunophilin

Mechanism: inhibit nuclear factor NFAT, production of IL-2, and 1st phase of T-cell activation

Uses: short and long term suppression of transplant rejection +CTS

ADR: 3N nephrotoxic 75%, neurotoxic 50%, neoplasm

7H hepatotoxicity

hypertension, hyperkalemia, hyperglycemia, hyperlipidemia

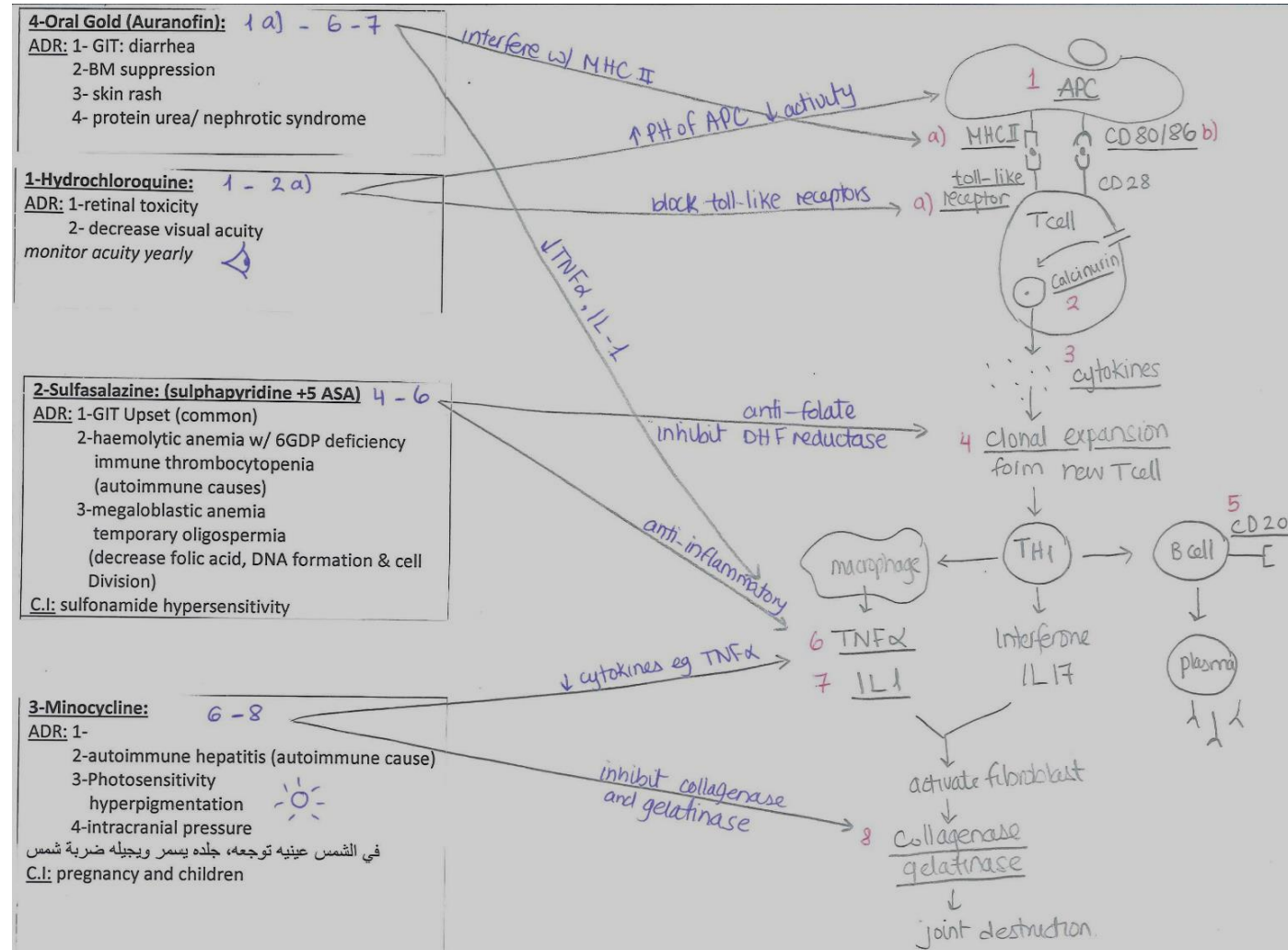
Hirsutism, hypertrophy of gums



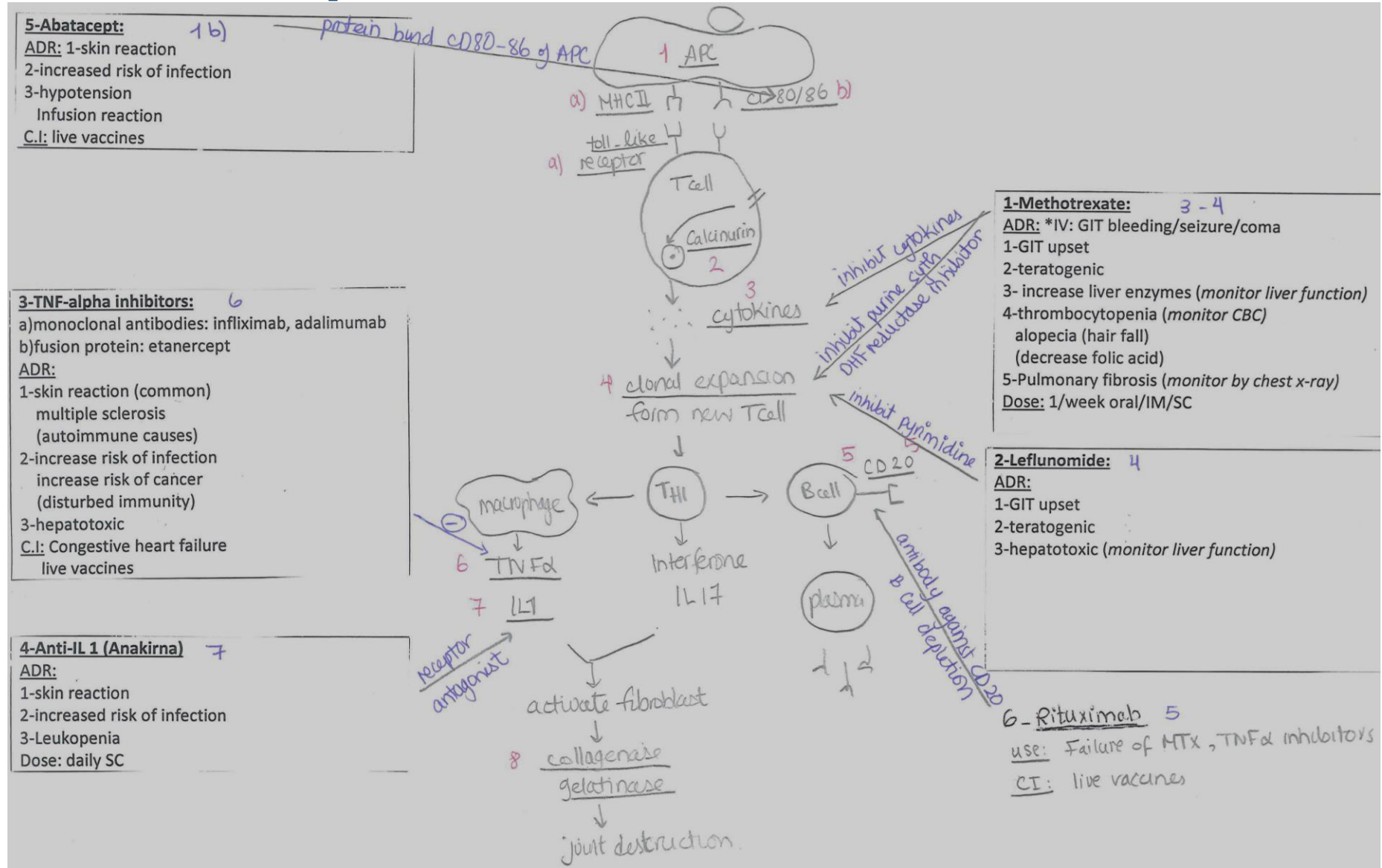


Treatment of Rheumatoid Arthritis

I. DMARDS useful for patients with early or mild Rheumatoid Arthritis:



II. DMARDs used for patients with moderate to severe Rheumatoid Arthritis:





Anti-cancerous drugs

1- Cell Cycle specific CCS: kill rapidly growing cells

2- Cell cycle non-specific CCNS: kill both slow and rapid cells

	Drug	Family	Mechanism	ADR	Notes
CCNS	Cyclophosphamide Ifosfamide	Alkylating Agents	Reactive species alkylate DNA at N7 of guanine on strands → break DNA	1-Nausea & vomiting 2-BM suppression 3-Hemorrhagic cystitis and bladder cancer	-CBC monitor -Rescue: Hydration and IV MESNA
	Doxorubicin	Antibiotic	1-Inhibit topoisomerase I 2-free radicals inhibit DNA formation	Cardiotoxic	
	Bleomycin		Free radicals	Pulmonary Fibrosis	
	Mitomycin (prod.)		Alkylate DNA		
CCS	Methotrexate	Anti-metabolite	DHF reductase inhibitor	1-Nausea & vomiting 2-BM suppression 3-Hepatotoxicity 4-Pulmonary Fibrosis	-CBC monitor -Rescue: Folinic acid (leucovorin)
	Mercaptopurine Thioguanidine		Antagonize purine		
	Fluorouracil (pro) Cytarabine(pro)		Antagonize pyrimidines -5FUMP → inhibit thymidylate synthase -CTP → inhibit polymerase		
	Vinca: Vincristine vinblastine	Plant alkaloids	Prevent microtubule polymerization at M-phase		
	Paclitaxel		Stabilize microtubules		
	Podophyllotoxins: Etoposide		Inhibit topoisomerase II at S and G2 phases		





Hormonal Agents:

- 1-Glucocorticoids(**prednisolone**): Blood cancers
- 2-SERM (**tamoxifen**): Breast cancer

Targeted Cancer Therapies:

- 1-Small molecules: target inside cell
- 2-monoclonal antibodies: target outside cell

Types: [SHAIMA + G]

- 1-Signal transduction
- 2-Hormone therapy
- 3-Apoptosis Inducers: controlled cell death
- 4-Immunotherapy: trigger immune system to destroy cancer cells
- 5-Monoclonal antibodies
- 6-Angiogenesis inhibitors: block growth of new blood vessels
- 7-Gene expression: modify function of proteins controlling gene expression

***Sorafenib:**

Mechanism:

- 1-block RAF kinase → inhibit cell division
- 2-inhibits vascular endothelial growth factor → inhibit angiogenesis

Use:

HCC (hepatocellular carcinoma), RCC (renal cell carcinoma), thyroid cancer

Resistance to drugs:

Decrease activation of drug	Change target enzyme
Increase inactivation of drug	Increase DNA repair
Decrease accumulation by multidrug resistance gene	Trapping agent e.g. reduced glutathione GSH





Goals of cancer chemotherapy:

- 1- Definitive: it's the main treatment e.g. non-solid cancer that can't be removed surgically
- 2- Adjuvant: in combination with surgery and radiotherapy
- 3- Palliative: decrease symptoms such as obstruction in terminal stage patients

Strategy:

- 1- Combination: decrease drug resistance and toxicity or side effects
- 2- Pulse therapy: every 3-4 weeks
- 3- Start with CCNS then CCS
- 4- Rescue therapy: save from toxicity

